IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVOZYMES A/S, Plaintiff, v. GENENCOR INTERNATIONAL, INC. and ENZYME DEVELOPMENT CORPORATION, Defendants.	)	C. A. No. 05-160-KAJ

PART 2

DEFENDANTS' PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW

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gene itself. (Alber, Tr. at 226:20-227:4, A-5227–5228, 232:9-11, A-5233, 303:4-9, A-5534.) Novozymes agrees. (Jorgensen, Tr. at 83:14-22, A-5083 (only the protein encoded by the DNA remains consistent over time.)) Thus, in contrast to a product protein (one that has been through industrial processing and/or fermentation), the mature or full-length protein (the protein encoded by the gene less the signal sequence) remains consistent over time and provides a certain basis for comparison.

I. "% Homology"

(1) The '031 Patent Does Not Require Use of the GAP (GCG) Program

186. The '031 Patent describes how "% homology" may be determined between two amino acid sequences:

> An amino acid sequence is considered to be X % homologous to the parent α-amylase, if a comparison of the respective amino acid sequences, performed via known algorithms, such as the one described by Lipman and Pearson in *Science* 227 (1985) p. 1435, reveals an identity of X %. The GAP computer program from the GCG package, version 7.3 (June 1993), may suitably be used, employing default values for GAP penalties [Genetic Computer Group (1991) Programme Manual for the GCG Package, version 7, 575 Science Drive, Madison, Wis., USA 53711].

(TE 100 at 9, col. 4:36-45, A-7009 (emphasis added.))

187. As described in this passage of the '031 Patent, "% homology" means the same thing as "% identity." (Devereux, Tr. at 124:22-25, A-5125, 128:9-13, A-5129; Arnold, Tr. at 140:6-14, A-5141; Alber, Tr. at 294:5-9, A-5525.) (Those terms are used interchangeably in these findings.)

188. According to this passage from the '031 Patent, aligning two amino acid sequences is a different step than calculating % identity. (Devereux, Tr. at 124:22-125:13, A-5125–5126.) First, one aligns the two sequences and, second, one calculates % identity using the alignment. (Devereux, Tr. at 126:9-12, A-5127; Arnold, Tr. at 145:14-20, A-5146; Alber, Tr. at 233:22-24, A-5234.)

189. When two sequences are very similar, one can use any alignment method and obtain the same alignment. (Devereux, Tr. at 126:1-3, A-5127.)

190. There is no dispute as to the proper alignment of the sequences here for purposes of determining infringement. (Arnold, Tr. at 142:1-6, A-5143; Alber, Tr. at 299:2-7, A-5530.)

191. The passage at column 4, lines 36-45 of the '031 Patent does not give complete instructions about how to calculate % homology. (Alber, Tr. at 233:1-16, A-5234.) It states that the percent homology is "revealed" from the alignment, but how the percent identity is "revealed" is ambiguous. (Alber, Tr. at 233:19-21, A-5234.)

192. The Lipman and Pearson algorithm identified in the passage does not disclose how to calculate % homology. (Alber, Tr. at 234:1-20, A-5235.)

193. The passage at column 4, lines 36-45 suggests that the GAP (GCG) program "may suitably be used." (Arnold, Tr. at 140:21-25, A-5124, 145:21-25, A-5146; TE 100 at 9, col. 4:40-42, A-7009.) However, it does not instruct a skilled protein engineer that the only program or method that may be used is the GAP (GCG) program (Devereux, Tr. at 128:19-129:6, A-5129–5130); another program may be used or the calculation may be performed by hand. (Alber, Tr. at 234:25-235:8, A-5235–5236.) Novozymes' expert Dr. Arnold agrees. (Arnold, Tr. at 181:12-182:10, A-5182–5183.)

194. Dr. Arnold admitted that there was not a pattern or practice amongst those of ordinary skill in the art regarding determination of percent homology. (Arnold, Tr. at 190:19-191:3, A-5191–5192.) In 1995, the GCG package made up 40% of the market of programs for sequence analysis. (Devereux, Tr. at 123:25-124:8, A-5124–5125.) As shown below, other programs and methods for sequence alignment and/or calculation of percent identity were available in 1995. (FF 215-220.) Novozymes' expert, Dr. Arnold, acknowledged that these other approaches might have given a different % homology calculation than the GAP (GCG) program. (Arnold, Tr. at 181:22-23, A-5182.)

(2) % Homology Obtained Using the GAP (GCG) Program

195. "X % identity" as calculated by GAP (GCG) does not mean that the sequences are X % identical; it means that they are X % identical over the regions where the sequences overlap. (Devereux, Tr. at 122:9-12, A-5123.)

196. Dr. Devereux testified that two amino acid sequences that are less than 100% identical due to "gaps" in the alignment would still have a 100% identity according to the GAP (GCG) program, because the program ignores differences due to such "gaps"—it ignores the deletion(s) of "gap" regions. (Devereux, Tr. at 116:10-117:7, A-5117–5118.) Commenting on this feature of the GAP (GCG) program, Dr. Alber stated that applying that approach to calculating % identity is not useful to one of ordinary skill in the art trying to apply the teachings of the '031 Patent. (Alber, Tr. at 235:9-21, A-5236.)

197. The GAP (GCG) program calculates % identity between two aligned sequences by taking the sum of all of the matching residues where there is a corresponding residue in both sequences, and counts the number of exact matches and divides that number by the number of residues where there are residues in both sequences. (Devereux, Tr. at 110:2-6, A-5111.) Thus, in calculating % identity, the GAP (GCG) program does not count "gaps," *i.e.*, regions where there is no residue in one sequence corresponding to a residue in the other sequence. (Devereux, Tr. at 111:9-12, A-5112.)

198. For example, when the GAP (GCG) program is used to calculate % identity between SPEZYME® Ethyl (TE 125, A-8345) and the protein sequence alleged by Novozymes for Genencor's G-ZYME® G997 product (TE 199, A-8529), the % identity is calculated to be 100%. (Devereux, Tr. at 112:14-113:20, A-5113–5114, 115:18-116:1, A-5116–5117; TE 126, A-8347.) Thus, the GAP (GCG) program computes 100% identity between these sequences despite that there is a "gap" (from two deletions) in the alignment where SPEZYME® Ethyl is missing two amino acids that are present in the

protein sequence alleged by Novozymes for Genencor's G-ZYME® G997 product (note the "gap" found at amino acids 179 and 180 of the G997 product). (TE 126, A-8347.)

199. One hundred percent (100%) identity would also be obtained with the GAP (GCG) program if one were to align two amino acid sequences that were identical, except that one extended beyond the end of the other, *i.e.*, one had an extended "tail." (Devereux, Tr. at 110:7-17, A-5110, 111:9-12, A-5111.) That would be so even if the "tail" were nearly a thousand amino acids longer than the sequence with which it was aligned, and even if the "tail" made a functional difference to the protein. (Devereux, Tr. at 121:10-25, A-5122, 122:1-4, A-5123, 122:23-123:6, A-5123–5124.)

200. The printout of the output GAP (GCG) program contains more than simply a number for % identity; it presents an actual visual comparison of the aligned sequences and shows how they "match up." (Devereux, Tr. at 129:8-21, A-5130; TE 127, A-8349–8350.) For example, the GAP (GCG) printout shows that the sequence of SEQ ID NO:3 is longer than the sequence of SPEZYME® Ethyl, *i.e.*, the sequences are of different length. (Devereux, Tr. at 129:18-130:14, A-5130–5131; TE 127 at 2, A-8350.)

(3) The '031 Patent Teaches the Skilled Artisan to Count All Sequence Differences

201. Because the deletion of the two amino acids at positions 179 and 180 is recited in the claims of the '031 Patent, those deletions are very important and should be counted in any % homology calculation. (Alber, Tr. at 237:22-25, A-5238.)

202. There are several passages in the '031 Patent that instruct the protein engineer to consider all types of sequence changes, including substitutions, insertions and deletions. (Alber, Tr. at 238:1-5, A-5239.) Dr. Borchert agreed these were the types of changes relevant to protein engineering. (Borchert, Tr. at 23:9-23, A-5023.)

203. For example, the '031 Patent states:

> The variants of the invention are variants in which: (a) at least one amino acid residue of the parent α-amylase has been deleted; and/or (b) at least one amino acid residue of the parent α-amylase has been replaced (i.e. substituted) by a different amino acid residue; and/or (c) at least one amino acid residue has been inserted relative to the parent α-amylase.

(TE 100 at 9, col. 3:59-65, A-7009 (emphasis added.))

204. This passage of the '031 Patent teaches a protein engineer of ordinary skill who is trying to figure out how to apply the results obtained from the GAP (GCG) program that even one amino acid that has been deleted should be counted in a % homology calculation. (Alber, Tr. at 238:20-239:7, A-5239–5240.)

205. In fact, the '031 Patent provides a nomenclature to describe all sequence differences, including deletions:

> Nomenclature
>
> In the present description and claims, the conventional one-letter codes for nucleotides and the conventional one-letter and three-letter codes for amino acid residues are used. For ease of reference, α-amylase variants of the invention are described by use of the following nomenclature:
>
> Original amino acid(s):position(s):substituted amino acid(s)
>
> According to this nomenclature, and by way of example, the substitution of alanine for asparagine in position 30 is shown as:
>
> Ala 30 Asn or A30N
>
> a deletion of alanine in the same position is shown as:
>
> Ala 30* or A30*
>
> and insertion of an additional amino acid residue, such as lysine, is shown as:
>
> Ala 30 AlaLys or A30AK
>
> A deletion of a consecutive stretch of amino acid residues, exemplified by amino acid residues 30-33, is indicated as (30-33)*.
>
> Where a specific α-amylase contains a "deletion" (i.e. lacks an amino acid residue) in comparison with other α-amylases and an insertion is made in such a position, this is indicated as:

*36 Asp or *36D

for insertion of an aspartic acid in position 36.

(TE 100 at 10, col. 6:36-62, A-7010 (emphasis added.))

206. This passage of the '031 Patent provides a nomenclature for defining deletions, insertions and substitutions. (Alber, Tr. at 239:8-11, A-5240.) Since the '031 Patent provides a nomenclature for specifying deletions, a protein engineer in 1995 reading the patent would have understood that it is necessary and important to count all deletions when calculating % homology. (Alber, Tr. at 239:12-16, A-5240, 295:6-297:24, A-5526–5528.)

207. In a prior Novozymes litigation concerning a related patent having the same specification, Dr. Arnold testified that in determining % homology one should take into account additions, substitutions and deletions. (TE 511 at 12, ¶ 30, A-8886; Arnold, Tr. at 185:7-21, A-5186.)

208. For all of these reasons, a skilled protein engineer in 1995 would count deletions, including terminal deletions, in calculating % homology according to the teachings of the '031 Patent.

(4) A Protein Engineer in 1995 Would Have Counted Deletions at the C-Terminus in Computing % Homology Between Alpha-amylases

209. Importantly, in addition to the teachings of the '031 Patent to count all deletions, a skilled protein engineer in 1995 would have considered changes to a protein that resulted from post-translational modifications to be sequence changes that are relevant to a comparison of the two sequences. (Alber, Tr. at 204:4-12, A-5205, 204:22-205:10, A-5205–5206.) In this regard, Dr. Arnold also admitted that, if the protein expressed from a "variant" gene is further truncated at its C-terminus, it is still a variant. (Arnold, Tr. at 176:19-177:13, A-5177–5178.) Specifically, in the case of comparing SPEZYME® Ethyl to an alleged "parent" in the claims of the '031 Patent, a skilled protein engineer in 1995 would have considered a truncation of amino acids at its C-terminus to be a sequence change in SPEZYME® Ethyl. (Alber, Tr. at 205:15-24, A-5206.)

210. The paper by Vihinen that was published in 1995 shows that the C-terminus of *Bacillus stearothermophilus* alpha-amylase is important for the enzymatic activity, *i.e.*, function, and stability of the alpha-amylase. (Alber, Tr. at 216:9-217:6, A-5217–5218, 217:20-218:20, A-5218–5219.)

211. This dependence of enzyme activity and stability on the full-length of the alpha-amylase provides a functional reason why a protein engineer in 1995 would have considered a *Bacillus stearothermophilus* alpha-amylase to be the "full-length" 514-515 amino acid protein encoded by the gene. (Alber, Tr. at 216:9-17, A-5217, 217:20-218:3, A-5218–5219.)

212. Knowing this dependence of enzyme activity and stability on the full-length of the alpha-amylase would have led a skilled protein engineer in 1995 to count deletions at the C-terminus regions when computing % homology between alpha-amylases. (Alber, Tr. at 218:21-219:2, A-5219–5220.)

(5) A Protein Engineer in 1995 Would Have Known How to Apply the Teachings of the '031 Patent to Calculate % Identity and Still Count Deletions

213. The '031 Patent's suggestion that one may suitably use the GAP (GCG) program, which ignores deletions, appears inconsistent with the teachings of the '031 Patent, which instructs one to count deletions in comparing a variant to its parent, and other evidence of the importance of considering deletions at the C-terminus in calculating % homology. (Alber, Tr. at 239:22-240:5, A-5240–5241.)

214. A skilled protein engineer in 1995, trying to follow the teachings of the '031 Patent, would have had several methods to resolve the apparent inconsistency (Alber, Tr. at 240:6-10, A-5241), all of which methods are consistent with the teachings of the '031 Patent. (Alber, Tr. at 241:5-16, A-5242.)

215. In 1995, methods other than the GAP (GCG) program were used to compute % homology, such as calculation "by hand" or use of other computer programs. (Arnold, Tr. at 181:17-182-10, A-5182–5183.)

216. The first such method that could resolve the apparent inconsistency is to use the GAP (GCG) to align the two sequences to be compared, and then calculate % identity by hand. (Alber, Tr. at 241:17-21, A-5242.) Dr. Devereux agreed that the GAP (GCG) program could be used in this manner. (Devereux, Tr. at 127:4-9, A-5128.) Using that "modified GAP (GCG) method" to compare SPEZYME® Ethyl to SEQ ID NO:3, one would take the number of residues that are identical in that alignment, which is 479, and divide it by the total number of residues in the 514-amino acid "parent" SEQ ID NO:3, *i.e.*, 479 divided by 514. (Alber, Tr. at 241:24-242:5, A-5242–5243.) This accounts for the entire C-terminal deletion of 30 residues of SPEZYME® Ethyl (as compared to its parent) and, thus, compares all of SPEZYME® Ethyl to all of SEQ ID NO:3. (Alber, Tr. at 242:6-11, A-5243.)

217. A second method is to use another computer program, named "Align," which was available in 1995 for doing an alignment and calculating % identity. (Alber, Tr. at 242:12-15, A-5243.) The Align program was publicly available as early as 1988 and was still available in 2005. (Pearson, Tr. at 310:22-311:12, A-5541–5542, 312:20-22, A-5543, 317:8-23, A-5548.) The Align program computes % identity by counting the number of identical amino acids in an alignment and dividing it by the number of amino acids that are included from the beginning of the left-most sequence to the end of the right-most sequences—the denominator includes the number of all of the amino acids in the alignment, such as the amino acids of an extension of one sequence beyond the end of the other sequence. (Pearson, Tr. at 314:5-315:15, A-5544–5545.)

218. A third method is to use another program available in 1995 for doing alignment and calculating % identity, named "GAP (Huang)." (Alber, Tr. at 242:17-22, A-5243.) The GAP (Huang) program was publicly available during the 1992-1994 time period. (Huang, Tr. at 333:15-334:23,

A-5564–5565, 334:5-18, A-5565, 336:25-337:4, A-5567–5568.) The GAP (Huang) program computes % identity by accounting for deletions and insertions, much like the Align program does. (Huang, Tr. at 338:3-10, A-5569.)

219. The difference between the GAP (GCG) program, on the one hand, and the Align and GAP (Huang) programs, on the other, is that they use a different formula for calculating % identity (Alber, Tr. at 242:19-22, A-5243.) The Align and GAP (Huang) programs count substitutions, additions, and deletions, thus counting all of the sequence differences in calculating % homology. (Alber, Tr. at 242:23-243:4, A-5243–5244.)

220. A fourth method is to do the alignment "by eye" and the calculation of % homology "by hand." (Alber, Tr. at 243:5-12, A-5244.) One would count the number of identical corresponding residues in the alignment and divide that by the total number of residues in the aligned sequences and use a calculator to get the answer. (Alber, Tr. at 243:9-12, A-5244.) Such "by eye" alignment between SPEZYME® Ethyl and SEQ ID NO:3 could have been done by a protein engineer of ordinary skill in 1995. (Alber, Tr. at 243:13-20, A-5244.)

221. A protein engineer seeking to apply all the teachings of the '031 Patent would use one of these four methods to calculate "% homology" as used in claims 1 and 3 of the '031 Patent.

(6) Appropriately Considering Deletions, SPEZYME® Ethyl is Less Than 95% Homologous to Each of SEQ ID NO:3 and a Properly Defined *Bacillus stearothermophilus* Alpha-amylase

(a) *Comparison to SEQ ID NO:3*

222. SPEZYME® Ethyl has a total of 484 amino acids (TE 127 at 2, A-8350) and SEQ ID NO:3 has a total of 514 amino acids. (TE 100 at 30, A-7030.) Looking at the GAP (GCG) program's printout (TE 127, A8349–8350), SEQ ID NO:3 has 5 amino acids that differ from SPEZYME® Ethyl in the alignment (ignoring "gaps"). Thus, there are 5 differences and 479 identical amino acids out of a total of 484 amino acids that align. 479/484 = .98967, or 99%.

223. In the "modified GAP (GCG)" method, the next step would be to add the number of amino acids of the "gap" regions, *i.e.* 30 (TE 127, A-8349–8350), into the denominator and re-do the quotient: 479/(484 + 30) = 479/514 = .9319, or 93.2%.

224. The same calculation would be implemented by both the Align and GAP (Huang) programs and in any "by hand" calculation. All would result in a % homology of less than 95%.

225. The reason that all of these methods arrive at a % homology of less than 95% is because they include all of the amino acids in the denominator of the calculation. Since SPEZYME® Ethyl is missing 30 amino acids due to truncation at the C-terminus in addition to the 179-180 "RG" deletion, counting those amino acids lowers the % homology to below 95%.

(b) *Comparison to Bacillus stearothermophilus alpha-amylase*

226. SPEZYME® Ethyl has a total of 484 amino acids (TE 127 at 2, A-8350) and the *Bacillus stearothermophilus* alpha-amylase of the "worst case" under Genencor's Alternate Construction has a total of 514 amino acids. When compared to a 514-amino acid sequence, SPEZYME® Ethyl would have 30 amino acids in "gap" regions, 2 from the 179-180 "RG" deletion and 28 from the deletion at the C-terminus. Doing the calculation of % homology "by hand," the numerator would be 484 (all of those amino acids are the same in both sequences) and the denominator would be 484 + 30 = 514. Thus, the calculation would be 484/(484 + 30) = 484/514 = .9416, or 94%.

227. The same calculation would be implemented by modified GAP (GCG) method and the Align and GAP (Huang) programs. All would result in a % homology of less than 95%. (Alber, Tr. at 245:2-18, A-5246.)

228. Again, the reason that all of these methods arrive at a % homology of less than 95% is because they include amino acids of the "gaps" in the denominator of the calculation. Since SPEZYME® Ethyl is missing 29 amino acids due to truncation at the C-terminus in addition to the

179-180 "RG" deletion, counting those amino acids lowers the % homology to below 95%. (Alber, Tr. at 246:9-247:2, A-5247–5248.)

229. Thus, whether in '031 Patent claims 1 and 3 "parent" and "*Bacillus stearothermophilus* alpha-amylase" mean "SEQ ID NO:3" or "the full-length, mature protein encoded by the DNA, minus the signal sequence," SPEZYME® Ethyl does not have the at least 95% homology required by those claims.

J. **Nonenablement**

(1) Computation of Number of Variants that Are 95% Homologous to SEQ ID NO:3 and Have the Required Double Deletion

230. Claim 1 of the '031 Patent recites a "variant of a parent *Bacillus stearothermophilus* alpha-amylase, wherein the variant has an amino acid sequence which has at least 95% homology to the parent *Bacillus stearothermophilus* alpha-amylase." (TE 100 at 40, col. 65:1-15, A-7040.) Claim 3 of the '031 Patent recites a "variant alpha-amylase, wherein the variant has at least 95% homology to SEQ ID NO:3." (TE 100 at 40, col. 65:21-66:11, A-7040.) Claims 1 and 3 both require a deletion of amino acid residues 179 and 180 of the parent alpha-amylase (using SEQ ID NO:3 for numbering) and that the variant have alpha-amylase activity. (TE 100 at 40, cols. 65:15-17, 66:10-12, A-7040.)

231. Approximately 10^{70} amino acid sequences have 95% homology to SEQ ID NO:3 and contain the required deletion of amino acid residues 179 and 180. (Alber, Tr. at 251:12-14, A-5252.) As a basis for comparison, the number of amino acid sequences that have 95% homology to SEQ ID NO:3 and contain the required double deletion is greater than the number of atoms in the Milky Way. (Alber, Tr. at 251:15-17, A-5252.)

232. In order to make a single alpha-amylase that is 95% homologous to SEQ ID NO:3, one of skill in the art would have to introduce appropriate nucleotide changes into a nucleic acid sequence encoding SEQ ID NO:3, express the protein encoded by the modified nucleic acid sequence, purify the protein, and test the protein for alpha-amylase activity and stability. (Alber, Tr. at 252:5-8, A-5253.)

It would take one of skill in the art longer than the age of the universe to produce a fraction of the 10^{70} amino acid sequences that have 95% homology to SEQ ID NO:3 and contain the required double deletion. (Alber, Tr. at 252:1-8, A-5253.)

(2) Estimation of Number of Variants Expected to Have Alpha-Amylase Activity

233. "[P]roteins are extremely complex and they are usually teetering on the brink of instability." (Arnold, Tr. at 707:25-708:1, A-6115–6116.) "[B]ecause they are fairly well designed to begin with, it is unfortunately much easier to damage one than it is to improve it." (Arnold, Tr. at 708:7-9, A-6116.) "[B]y far the most common result" of randomly changing the sequence of a protein "is that you would degrade its properties." (Arnold, Tr. at 135:22-136:2, A-5136–5137.) In fact, "changing even a single amino acid" in the sequence of a protein "can often have a deleterious effect." (Arnold, Tr. at 136:3-7, A-5137.)

234. Only a small fraction of random sequence changes to SEQ ID NO:3 would produce a protein with alpha-amylase activity and stability. (Alber, Tr. at 252:15-17, A-5253.) Most of such changes to SEQ ID NO:3 would reduce its alpha-amylase activity or stability. (Alber, Tr. at 252:13-15, A-5253; Borchert, Tr. at 24:5-16, A-5024.)

235. A maximum of 1 in 10,000 amino acid sequences that are 95% homologous to SEQ ID NO:3 and contain a deletion of amino acid residues 179 and 180 of SEQ ID NO:3 would have alpha-amylase activity. (Alber, Tr. at 252:17-20, A-5253.)

236. The '031 Patent provides no general guidance to determine which sequence changes in SEQ ID NO:3 would result in proteins that are 95% homologous to SEQ ID NO:3, contain the required double deletion, and have alpha-amylase activity. It merely provides a handful of examples of such sequence changes and instructs one of skill in the art to subject a DNA sequence encoding a parent alpha-amylase to random mutagenesis, express the mutated DNA sequence in a host cell, and screen

for host cells expressing a mutated amylolytic enzyme which has improved properties as compared to the parent alpha-amylase. (TE 100 at 10, col. 6:18-33, A-7010.)

237. The number of examples of mutations taught by the '031 Patent are an insignificant fraction of the possible amino acid sequences that are 95% homologous to SEQ ID NO:3, contain the required double deletion, and have alpha-amylase activity. (Alber, Tr. at 253:8-9, A-5253.) "Essentially a trillionth of a trillionth of a trillionth" of the possible amino acid sequences encompassed by the claims are enabled by the '031 Patent. (Alber, Tr. at 253:9-11, A-5254.)

III. PROPOSED CONCLUSIONS OF LAW

A. Non-Infringement

(1) Legal Standard for Infringement/Claim Construction

1. Novozymes bears the burden of proving infringement by a preponderance of the evidence. *See Ultra-Tex Surfaces, Inc. v. Hill Bros. Chem. Co.*, 204 F.3d 1360, 1364 (Fed. Cir. 2004). Determining patent infringement involves two basic steps: (1) properly construing the claims to determine their meaning and scope, which is a question of law, and (2) comparing the properly construed claims with the accused product to determine if there is infringement, which is a question of fact. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995), *aff'd*, 517 U.S. 370 (1996).

2. Claim terms are generally given their ordinary and customary meaning, as understood by one of ordinary skill in the art at the time of the invention when read in view of the patent specification. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13, 1321 (Fed. Cir. 2005), *cert. denied*, 126 S. Ct. 1332 (2006); *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

3. The ordinary meaning of a claim term is its meaning to the skilled artisan after reading the entire patent. *See Phillips*, 415 F.3d at 1321. Therefore, the claims must be read in view of the patent specification of which they are a part. "[T]he specification 'is always highly relevant to the

claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.'" *Id.* at 1315 (quoting *Vitronics*, 90 F.3d at 1582). "[T]he specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess. In such cases, the inventor's lexicography governs." *Phillips*, 415 F.3d at 1316. *See also Vitronics*, 90 F.3d at 1582. In fact, the Federal Circuit has specifically cautioned against placing too much emphasis on the ordinary meaning of a term without adequate consideration of that term within the context of the patent specification. *See Curtiss-Wright Flow Control Corp. v. Velan, Inc.*, 438 F.3d 1374, 1378-79 (Fed. Cir. 2006); *On Demand Machine Corp. v. Ingram Indus., Inc.*, No. 05-1074, 2006 WL 827302, at *4 (Fed. Cir. March 31, 2006) (noting that *Phillips* "stressed the dominance of the specification in understanding the scope and defining the limits of the terms used in the claim"). Where the specification contains multiple possible definitions of a claim term, the definition most reasonably relied upon by the Examiner in allowing the claims should control. *See Genentech, Inc. v. Wellcome Found. Ltd.*, 29 F.3d 1555, 1564-65 (Fed. Cir. 1994).

4. Courts also review the prosecution history of a patent for evidence regarding the proper construction of claim limitations. *See Phillips*, 415 F.3d at 1317; *Vitronics*, 90 F.3d at 1582-83. The prosecution history can often inform the meaning of claim language by demonstrating how the inventor understood the invention and whether the inventor limited the scope of the claims during the course of prosecution to obtain claim allowance. *See, e.g., Phillips*, 415 F.3d at 1317; *Athletic Alternatives, Inc. v. Prince Mfg., Inc.*, 73 F.3d 1573, 1579-80 (Fed. Cir. 1996). It is axiomatic that a patentee cannot advance a narrow definition during prosecution to secure claim allowance and then advance a broader definition to encompass alleged infringers. *See, e.g., Research Plastics, Inc. v. Federal Packaging Corp.*, 421 F.3d 1290, 1298 (Fed. Cir. 2005); *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1576 (Fed. Cir. 1995). Where the prosecution history reflects that the patentee disclaimed or disavowed a claim interpretation, the claims are to be construed so as to exclude any

such interpretation. *See Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 998 (Fed. Cir. 2006) (finding applicants' statements distinguishing their claimed materials over prior art during prosecution constitute a disclaimer of claim scope); *Revolution Eyewear, Inc. v. Aspex Eyeware, Inc.*, No. 05-1329, 2006 WL 870689, at *6 (Fed. Cir. March 30, 2006). The patentee may not base an infringement claim of claim scope disavowed in prosecution. *See Terlep v. Brinkmann Corp.*, 418 F.3d 1379, 1385-86 (Fed. Cir. 2005).

5. Of course, a narrow disclosure may, by itself, limit the scope of the claims, which can be no broader in scope than the invention disclosed in and enabled by the specification. *See On Demand*, 2006 WL 827302, at *7. The Federal Circuit has repeatedly re-affirmed that "[t]he construction that stays true to the claim language and most naturally aligns with the patent's description of the assertion will be, in the end, the correct construction." *Nystrom v. TREX Co.*, 424 F.3d 1136, 1142 (Fed. Cir. 2005) (citing *Phillips*, 415 F.3d at 1316; internal quotations and citations omitted), *cert. denied*, 2006 WL 236242 (Apr. 3, 2006)). Even without a clear disavowal of claim scope, use of a term consistently in the intrinsic record supports a construction narrower that might have advanced based on extrinsic evidence, such as dictionaries. *See Nystrom*, 424 F.3d at 1145.

6. Extrinsic evidence, which consists of all evidence external to the patent and its prosecution history, such as dictionaries, treatises, and expert testimony, also may be used by the Court to understand the technology of the patent and to explain terms of art. *See Phillips*, 415 F.3d at 1317-18; *Vitronics*, 90 F.3d at 1583-84. However, as noted above, extrinsic evidence "is unlikely to result in a reliable interpretation of patent claim scope unless considered in the context of the intrinsic evidence." *Phillips*, 415 F.3d at 1319, 1320. The Federal Circuits has cautioned especially strongly against the use of extrinsic evidence to improperly expand claim scope:

> Broadening of the ordinary meaning of a term in the absence of support in the intrinsic record indicating that such a broad meaning was intended violates the principles articulated in *Phillips*.

Nystrom, 424 F.3d at 1145-46.

7. "[C]laim drafters can ... use different terms to define the exact same subject matter. Indeed this court has acknowledged that two claims with different terminology can define the exact same subject matter." *Curtiss-Wright Flow Control*, 438 F.3d at 1380-81 (citing *Tandon Corp. v. U.S. Int'l Trade Comm'n*, 831 F.2d 1017, 1023 (Fed. Cir. 1987)). *See also Hormone Research Found., Inc. v. Genentech, Inc.*, 904 F.2d 1558, 1567 n.15 (Fed. Cir. 1990) ("It is not unusual that separate claims may define the invention using different terminology, especially where (as here) independent claims are involved."). Indeed, the Federal Circuit has "cautioned that '[c]laim differentiation is a guide, not a rigid rule.'" *Curtiss-Wright Flow Control*, 438 F.3d at 1381 (quoting *Laitram Corp. v. Rexnord, Inc.*, 939 F.2d 1533, 1538 (Fed. Cir. 1991)). Thus, while claims in a patent are presumed to be of different scope, the doctrine of claim differentiation does not override the construction of claim terms in light of the specification and prosecution history:

> However, simply noting the difference in the use of claim language does not end the matter. Different terms or phrases in separate claims may be construed to cover the same subject matter where the written description and prosecution history indicate that such a reading of the terms or phrases is proper.

Nystrom, 424 F.3d at 1143. *See also Multiform Dessicants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1479-80 (Fed. Cir. 1998). Importantly, claim differentiation "can not broaden claims beyond their correct scope." *Kraft Foods, Inc. v. International Trading Co.*, 203 F.3d 1362, 1368 (Fed. Cir. 2000) (quoting *Multiform Dessicants*, 133 F.3d at 1480). It is well-established that the written description and prosecution history override any presumption arising from the doctrine of claim differentiation. *See Fantasy Sports Props., Inc. v. Sportsline.com, Inc.*, 287 F.3d 1108, 1115-16 (Fed. Cir. 2002) (citing *Kraft Foods*, 203 F.3d at 1368-69).

8. Once the claim terms are construed, literal infringement is present only when each and every element set forth in the patent claims is found in the accused product. *See, e.g., Southwall*

Techs., 54 F.3d at 1575-76. Pursuant to this Court's grant of Genencor's Motion *In Limine* Re: Doctrine of Equivalents, Novozymes may not raise the issue of infringement under the doctrine of equivalents. (Updated Proposed Final Pretrial Order, D.I. 101 at section IX.B.2.)

(2) Claim Construction of '031 Patent

9. There is no dispute as to the meaning of the terms "variant" (claims 1, 3, and 5) and "parent" (claim 1). A "variant" protein is one that has been derived from a "parent" protein by human manipulation of (genetically engineering) the DNA encoding the parent protein so as to substitute, insert, or delete amino acids in the variant protein relative to the parent protein. (FF 15.)

10. There is no dispute that the term "*Bacillus stearothermophilus*" of claims 1 and 5 refers to a wild type *Bacillus stearothermophilus* bacterium. (FF 14.)

11. There is no dispute that the use of the phrase "consisting of" in claim 5 means that any product accused of infringement of claim 5 may contain only those variations specifically identified in claim 5. (Arnold, Tr. at 146:12-23, A-5147; Alber, Tr. at 246:3-9, A-5247.) *See Norian Corp. v. Stryker*, 363 F.3d 1321, 1331-32 (Fed. Cir. 2004).

12. Based on the evidence set forth above (FF 135-142), when considered together with the specification of the '031 Patent and statements of the applicants and Examiner in prosecution of the '031 Patent, the term "*Bacillus stearothermophilus* alpha-amylase" in claims 1 and 5 means "an alpha-amylase having the amino acid sequence of SEQ ID NO:3" ("Genencor's Construction"). As set forth above, Novozymes may not rely on a definition of "*Bacillus stearothermophilus* alpha-amylase" in litigation broader than that which it asserted in prosecution to assure issuance of the '031 Patent. *See Research Plastics*, 421 F.3d at 1298; *Phillips*, 415 F.3d at 1317. The Court is compelled, by Novozymes' statements in prosecution, to limit "*Bacillus stearothermophilus* alpha-amylase" to "SEQ ID NO:3," because this is the definition Novozymes advanced, and on which the Examiner relied, in prosecution of the '031 Patent. *See id.*; *Genentech*, 29 F.3d at 1564-65.

13. Genencor has presented an alternate construction of the term "*Bacillus stearothermophilus* alpha-amylase" for claims 1 and 5 in the event that the construction of the preceding paragraph is not selected. By that alternate construction, based on the evidence set forth above (FF 143-166), consistent with the teachings of the '031 Patent and the literature, the term "*Bacillus stearothermophilus* alpha-amylase" means a 514- or 515-amino acid protein encoded by a wild type *Bacillus stearothermophilus* alpha-amylase gene, minus the signal sequence ("Genencor's Alternate Construction"). This alternate construction satisfies the Federal Circuit's mandate to seek a construction giving claim terms, such as "*Bacillus stearothermophilus* alpha-amylase," their ordinary and customary meaning to an ordinary skilled protein engineer in 1995. *See Phillips*, 415 F.3d at 1312-13.

14. The Court rejects Novozymes' assertion that "*Bacillus stearothermophilus* alpha-amylase" as used in the '031 Patent means or refers to a protein sold as a commercial product or otherwise subjected to conditions such as industrial processing and fermentation. As described above (FF 169-171), the sequence of such proteins is demonstrably variable over time and between different samples. Because certainty of the sequence of the "*Bacillus stearothermophilus* alpha-amylase" is required to reliably make the comparison to any accused product, construing that term in a manner that leaves it variable and uncertain would render the claim indefinite and invalid under 35 U.S.C. § 112. *See Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1384 (Fed. Cir. 2003).

15. The Court also rejects Novozymes' argument that so-called claim differentiation requires any different definition of "*Bacillus stearothermophilus* alpha-amylase" in claims 1 and 3 of the '031 Patent. As described above, Novozymes relied on a definition of "*Bacillus stearothermophilus* alpha-amylase" to mean "SEQ ID NO:3" to obtain the '031 Patent, overriding any "presumption" that "*Bacillus stearothermophilus* alpha-amylase" does not mean "SEQ ID NO:3." *See Fantasy Sports*, 287 F.3d at 1115-16. As the Federal Circuit has made clear, "two claims with

different terminology can define to exact same subject matter." *Curtiss-Wright Flow Control*, 438 F.3d at 1380-81. That is what has happened here, as a result of Novozymes' statements in prosecution.

16. For purposes of determining "at least 95% homology," there is no dispute as to the amino acid sequence alignment of the variant and parent alpha-amylases identified in the claims. (FF 186-198.) When considered together with the specification of the patent and statements of the applicants and Examiner in the file history (FF 201-208), the term "at least 95% homology" of claims 1 and 3 requires use of any method that accounts for all substitutions, insertions, and deletions, including internal and terminal deletions, over the entire amino acid sequences of the variant and parent alpha-amylases identified in the claims. This construction is compelled for two reasons. First, the '031 Patent specification, taken as a whole, clearly teaches that all deletions, including deletions at the C-terminus, should be counted in determining % homology. *See On Demand*, 2006 WL 827302, at *4 (stressing "dominance of the specification in understanding the scope and determining the limits of the terms used in the claims"). Second, one of skill in the art in 1995 would have considered deletions at the C-terminus to have functional relevance to thermostability, supposedly core to the '031 Patent, and would therefore have counted such deletions for determining % homology. (FF 209-212.) *See Phillips*, 425 F.3d at 1312-13.

17. There is no dispute as to the meaning in claims 1, 3, and 5 of the phrase "a deletion of amino acids 179 and 180, using SEQ ID NO:3 for numbering," one aligns the amino acid sequence of the allegedly infringing variant with the amino acid sequence of SEQ ID NO:3 and determines whether the two consecutive amino acids, arginine and glycine, or "RG," are absent at positions corresponding to positions 179 and 180 of SEQ ID NO:3. (FF 186-188.) For purposes of determining whether the phrase "a deletion of amino acids 179 and 180, using SEQ ID NO:3 for numbering" is satisfied, there is no dispute as to the amino acid sequence alignment of the variant and parent alpha-amylases of the claims. (FF 190.)

18. There is no dispute that "alpha-amylase activity" of claims 1 and 3 means the ability to catalyze the cleavage of starch to smaller sugar molecules. (FF 18.)

(3) Making, Using, Importing, Selling, or Offering to Sell SPEZYME® Ethyl Does Not Infringe Claim 1 of the '031 Patent

(a) *Genencor's construction of "Bacillus stearothermophilus alpha-amylase"*

19. SPEZYME® Ethyl is a "variant of a parent *Bacillus stearothermophilus* alpha-amylase," comprising a deletion of amino acids 179 and 180, using SEQ ID NO:3 for numbering, because it is missing the two amino acids, arginine and glycine, at positions corresponding to positions 179 and 180 of SEQ ID NO:3. (FF 52.)

20. SPEZYME® Ethyl has alpha-amylase activity. (FF 52.)

21. If the phrase "*Bacillus stearothermophilus* alpha-amylase" in claim 1 means "SEQ ID NO:3," then claim 1 is not infringed by SPEZYME® Ethyl because its amino acid sequence does not have "at least 95% homology" to SEQ ID NO:3 using any appropriate method that accounts for all substitutions, insertions, and deletions, including internal and terminal deletions, over the entire amino acid sequence alignment. As set forth above (FF 222-225), calculating % homology between the amino acid sequences of SPEZYME® Ethyl and SEQ ID NO:3 by "GAP (GCG) modified," by the Align program, by the GAP (Huang) program, or "by hand," one always obtains a % homology that is less than 95%. (Alber, Tr. at 245:2-7, A-5246.)

22. Because SPEZYME® Ethyl does not satisfy the limitation of claim 1 that it have "at least 95% homology" to SEQ ID NO:3 (Genencor's Construction), claim 1 is not infringed.

(b) *Genencor's alternate construction of "Bacillus stearothermophilus alpha-amylase"*

23. The only difference between Genencor's Construction and its Alternate Construction is the definition of the term "*Bacillus stearothermophilus* alpha-amylase."

24. Under Genencor's Alternate Construction, the term "*Bacillus stearothermophilus* alpha-amylase" means a 514- or 515-amino acid protein encoded by a wild type *Bacillus stearothermophilus* alpha-amylase gene, minus the signal sequence. Note that there is no single amino acid sequence specified because it is a genus of related alpha-amylases. For purposes of this analysis, therefore, the "worst case" will be assumed in which (a) the alpha-amylase has 514 amino acids (a 515 amino acid protein where the additional position is a deletion would lower the % homology) and (b) the amino acid sequence is identical to that of SPEZYME® Ethyl, except for the positions of the 179-180 "RG" deletion and truncation at the C-terminus (such identity would give the highest % homology).

25. As set forth above (FF 226-229), calculating % homology between the amino acid sequences of SPEZYME® Ethyl and the 514-amino acid protein of the "worst case" under Genencor's Alternate Construction by "GAP (GCG) modified," by the Align program, by the GAP (Huang) program, or by hand, one always obtains a % homology that is less than 95%. (Alber, Tr. at 245:8-18, A-5246.)

26. Because SPEZYME® Ethyl does not satisfy the limitation of claim 1 that it have "at least 95% homology" to the "worst case" under Genencor's Alternate Construction, claim 1 is not infringed.

(4) Making, Using, Importing, Selling, or Offering to Sell SPEZYME® Ethyl Does Not Infringe Claim 3 of the '031 Patent

27. SPEZYME® Ethyl is a variant alpha-amylase comprising a deletion of amino acids 179 and 180, using SEQ ID NO:3 for numbering, because it is missing the two amino acids, arginine and glycine, at positions corresponding to positions 179 and 180 of SEQ ID NO:3. (FF 52.)

28. SPEZYME® Ethyl has alpha-amylase activity. (FF 52.)

29. The % homology between SPEZYME® Ethyl and SEQ ID NO:3 is calculated in FF 222-225 above. Using any appropriate method that accounts for all substitutions, insertions, and deletions, including internal and terminal deletions, over the entire amino acid sequence alignment,

SPEZYME® Ethyl does not have "at least 95% homology" to SEQ ID NO:3. (Alber, Tr. at 247:19-24, A-5248.)

30. Because SPEZYME® Ethyl does not satisfy the limitation of claim 3 that it have "at least 95% homology" to SEQ ID NO:3, claim 1 is not infringed.

(5) Making, Using, Importing, Selling or Offering to Sell SPEZYME® Ethyl Does Not Infringe Claim 5 of the '031 Patent

31. SPEZYME® Ethyl is a variant of a *Bacillus stearothermophilus* alpha-amylase because it was initially developed by human modification of (genetically engineering) the DNA encoding the alpha-amylase of the *Bacillus stearothermophilus* strain G997, which encodes a 515-amino acid protein (after removal of the signal sequence). (FF 54-56.) That 515-amino acid alpha-amylase encoded by the alpha-amylase gene of strain G997 is the "parent" of SPEZYME® Ethyl. (FF 57.) That "parent" is a wild type *Bacillus stearothermophilus* alpha-amylase. (FF 57.)

32. Claim 5 recites that "the alpha-amylase variant consists of a deletion of amino acids 179 and 180, using SEQ ID NO:3 for numbering." (TE 100 at 40, col. 66:18-20, A-7040.) This means that the claim permits the deletion of amino acids 179 and 180 to be the only difference between the alleged infringing product and its parent. (Arnold, Tr. at 146:12-23, A-5147; Alber, Tr. at 248:3-9, A-5249.) *See Norian*, 363 F.3d at 1331-32.

(a) *Genencor's construction of "Bacillus stearothermophilus alpha-amylase"*

33. If the phrase "*Bacillus stearothermophilus* alpha-amylase" in claim 5 means "SEQ ID NO:3," then claim 5 is not infringed because, when one compares the amino acid sequence of SPEZYME® Ethyl to that of SEQ ID NO:3, SPEZYME® Ethyl has changes in addition to the deletion of amino acids 179 and 180 that are different from SEQ ID NO:3. (Alber, Tr. at 248:10-19, A-5249.) Those other changes are five different amino acid substitutions throughout the body of the protein and

the deletion of 30 amino acids from the C-terminus of SEQ ID NO:3. (Alber, Tr. at 248:19-21, A-5249.)

34. Because SPEZYME® Ethyl does not satisfy the limitation of claim 5 that it "consist of" a deletion of amino acids 179 and 180 when compared to the amino acid sequence of SEQ ID NO:3, claim 5 is not infringed.

(b) *Genencor's alternate construction of "Bacillus stearothermophilus alpha-amylase"*

35. The only difference between Genencor's Construction and its Alternate Construction is the definition of the term "*Bacillus stearothermophilus* alpha-amylase."

36. Under Genencor's Alternate Construction, the term "*Bacillus stearothermophilus* alpha-amylase" means a "full-length," 514- or 515-amino acid protein encoded by a wild type *Bacillus stearothermophilus* alpha-amylase gene (minus the signal sequence of the preprotein). Note that there is no single amino acid sequence specified, because it is a genus of related alpha-amylases. For purposes of this analysis, therefore, the "worst case" will be assumed in which the amino acid sequence of the *Bacillus stearothermophilus* alpha-amylase is identical to that of SPEZYME® Ethyl except for the positions of the 179-180 "RG" deletion and a truncation at the C-terminus of about 30 amino acids.

37. If the phrase "*Bacillus stearothermophilus* alpha-amylase" in claim 5 means the protein of the "worst case" under Genencor's Alternate Construction, then claim 5 is not infringed because, when one compares the amino acid sequence of SPEZYME® Ethyl to any 514 or 515 amino acid wild type *Bacillus stearothermophylus* alpha-amylase, SPEZYME® Ethyl contains at least the deletion of 30 or 31 amino acids at the C-terminus in addition to the deletion of amino acids 179 and 180. (Alber Tr. at 248:22-249:2, A-5249–5250.)

38. Because SPEZYME® Ethyl does not satisfy the limitation of claim 5 that it "consist of" a deletion of amino acids 179 and 180 when compared to a 514- to 515-amino acid wild type *Bacillus stearothermophylus* alpha-amylase, claim 5 is not infringed.

(6) Even Under its Own Proposed Constructions, Novozymes Has Failed to Meet its Burden of Proof to Show Infringement by SPEZYME® Ethyl as Manufactured in September 2, 2005

39. As described above, SPEZYME® Ethyl is currently produced from a genetically engineered DNA which terminates translation of the alpha-amylase 28 amino acids short of the point at which translation stops during expression of the "full-length" protein from a wild type *Bacillus stearothermophilus* gene. (FF 56-58.) Novozymes has offered no proof, including expert testimony, as to infringement by SPEZYME® Ethyl as manufactured since September 2, 2005, using this "New DNA Sequence." (FF 56.) Therefore, for this independent reason, regardless of the Court's claim construction, Novozymes has failed to meet its burden to show infringement by SPEZYME® Ethyl since September 2, 2005; judgment is to be entered for Genencor to that extent.

(7) Novozymes Cannot Meet its Burden of Proof to Show Infringement if G-ZYME® G997 is the "Parent" to which SPEZYME® Ethyl Must Be Compared

40. As described above, Novozymes has presented the Court with at least four different amino acid sequences produced from DNA encoding the same alpha-amylase, *i.e.*, produced from the wild type genes of *Bacillus stearothermophilus* strains G997 and ATCC 31,195. (FF 178-185.) Claims 1, 3, and 5 of the '031 Patent require a comparison of the amino acid sequence of the alleged "parent" with the amino acid sequence of the accused product. Because the amino acid sequence of G-ZYME® G997 is uncertain and variable, as described above (FF 178-185), it is impossible to make a mathematically or otherwise certain comparison of the amino acid sequence of G-ZYME® G997 to any accused product, including SPEZYME® Ethyl. Thus, Novozymes cannot meet its burden to show

infringement by SPEZYME® Ethyl if G-ZYME® G997 is the "parent." Because that is Novozymes' assertion, it cannot show infringement; judgment is therefore to be entered for Genencor.

B. **Claims 1, 3, and 5 of the '031 Patent Are Invalid**

(1) Claims 1, 3, and 5 Are Invalid as Obvious in Light of Prior Art

(a) *Legal standard*

41. Genencor bears the burden to prove obviousness, a question of law based on underlying factual findings, by clear and convincing evidence. *See In re Kahn*, 441 F.3d 977, 985 (Fed. Cir. 2006); *In re GPAC Inc.*, 57 F.3d 1573, 1582 (Fed. Cir. 1995).

42. In determining whether a claim is invalid as obvious under 35 U.S.C. § 103(a), the court should consider: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) objective indicia of nonobviousness. *See Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1372-73 (Fed. Cir.), *cert. denied*, 126 S. Ct. 488 (2005) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)). Obviousness does not require absolute predictability but, rather, a reasonable expectation of success. *See In re O'Farrell*, 853 F.2d 894, 903-904 (Fed. Cir. 1988).

43. Where, as with Suzuki and the Bisgard-Frantzen PCT, obviousness is based on a combination of references, the question is whether one of skill in the art would have been motivated to combine them. *See In re Kahn,* 441 F.3d at 987. If one of ordinary skill, confronted with the same problem as the '031 inventors and without knowledge of their alleged invention, would have selected and combined the prior art references to achieve the invention of the '031 Patent, the combination is proper and the patent obvious. *See id.*; *Princeton Biochems., Inc. v. Beckman Coulter, Inc.*, 411 F.3d 1332, 1338 (Fed. Cir. 2005). It is not necessary for the prior art to expressly suggest the combination; rather, cross-referencing a prior art reference, along with the nature of the problem to be solved and the

knowledge of the skilled artisan, may suffice to show obviousness based on a combination of references. *See In re Johnston*, 435 F.3d 1381, 1384-85 (Fed. Cir. 2006) (and citations).

44. Novozymes concedes (as it did in prosecution) that the '031 Patent is *prima facie* obvious based on the combination of Suzuki and the Bisgard-Frantzen PCT. Moreover, Novozymes elected to avoid the pending rejection of '031 claims to seek allowance of claims based on alleged non-obviousness compared to Suzuki and the Bisgard-Frantzen PCT. Novozymes thus bears the burden to rebut the obviousness of the asserted '031 claims as against Suzuki and the Bisgard-Frantzen PCT. *See In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991).

45. To the extent Novozymes intends to rely on the Borchert Declaration to prove non-obviousness, Novozymes bears the burden "of explaining the data in any declaration [proferred] as evidence of non-obviousness." *Ex parte Ishizaka*, 24 U.S.P.Q. 2d at 1624. When, as here, "unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *In re Baxter*, 952 F.2d at 392. *See also In re Mayne*, 104 F.3d 1339, 1341-42 (Fed. Cir. 1997); MPEP §§ 716.02(b), 716.02(e). Where there are deviations between the closest prior art and the circumstances giving rise to the alleged unexpected results, the deviations should be identified and explained, especially if the deviations are significant. *See* MPEP § 716.02(e) (and citations).

46. Evidence offered to show unexpected results may be insufficient to overcome the teachings of the prior art. *See Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1484 (Fed. Cir. 1997); *In re Eli Lilly & Co.*, 902 F.2d 943, 946-48 (Fed. Cir. 1990) (holding that data offered as showing unexpected results did not outweigh the clear teaching of the prior art); *In re Nolan*, 553 F.2d 1261, 1266-67 (C.C.P.A. 1977). Even where there is evidence of nonobviousness, such as allegedly unexpected results, the record may also establish such a strong case of obviousness that even that the objective evidence of nonobviousness is not sufficient to outweigh the finding of obviousness. *See*

Richardson-Vicks, 122 F.3d at 1484; *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 769 (Fed. Cir. 1988), *cert. denied*, 493 U.S. 814 (1989). The Court may properly consider evidence from the relevant technical field to determine whether results presented to rebut obviousness are "truly unexpected" and whether differences revealed in experiments are sufficiently appreciable to be unexpected. *See In re Merck Co., Inc.*, 800 F.2d 1091, 1099 (Fed. Cir. 1988). Where differences revealed in comparative testing are a "matter of degree rather than kind," the alleged unexpected results will not overcome the finding of obviousness. *Id.* In addition, the evidence of unexpected results must be commensurate with the scope of the claims the evidence is offered to support. *See In re Greenfield*, 571 F.2d 1185, 1189 (C.C.P.A. 1978).

(b) *The combination of Suzuki/Bisgard-Frantzen renders obvious the asserted claims*

47. During prosecution of the '031 Patent, Examiner Prouty rejected the claimed BSG alpha-amylase as *prima facie* obvious over Suzuki in view of the Bisgard-Frantzen PCT. (FF 24-28.)

48. Novozymes' expert Dr. Arnold admitted that Suzuki would have provided the impetus for a protein engineer to make the deletion of residues 179 and 180 in BSG; thus, she admitted that Suzuki made the claimed deletion *prima facie* obvious. (FF 167.)

49. The obviousness of the '031 Patent in view of Suzuki is further evidenced by the fact that it was Suzuki's teachings which provided Genencor with the impetus to make the 179-180 deletion in a *Bacillus stearothermophilus* alpha-amylase. (Crabb, Tr. at 40:11-41:7, A-5040–5041.)

50. Novozymes never challenged (in prosecution or at trial) the obviousness of the '031 Patent in view of Suzuki and the Bisgard-Frantzen PCT. Instead, in response to the Examiner's rejection based on Suzuki and the Bisgard-Frantzen PCT, Novozymes submitted narrowed claims in order "to buy time," as explained above. (FF 37-39.) Then, after, Novozymes had conducted the alleged "experiment," it took back the narrowed claims and presented the "unexpected results" against Suzuki and the Bisgard-Frantzen PCT, even though that rejection had not been pending for months. In

other words, Novozymes executed and attacked a "straw man," by attacking Suzuki instead of the closest (and undisclosed) prior art, Machius '95.

51. Novozymes did so by submitting to the PTO a Declaration under 37 C.F.R. § 1.132 by inventor Dr. Torben Borchert in the prosecution of the '031 Patent to obtain broader claims (even though the Suzuki rejection was not pending at the time). (FF 46, 100.) The Borchert Declaration allegedly showed that the BSG alpha-amylase with a deletion of amino acids 179 and 180 was unexpectedly more thermostable than BAN having the same deletion.

52. Even considered on its "merits," the Borchert Declaration fails to overcome the admitted *prima facie* case of obviousness, for many reasons.

53. Initially, one of ordinary skill in the art would not have been surprised by Dr. Borchert's alleged results with BSG, nor found these results to be different in kind nor unexpected, because these alleged results showed improvement in BSG in the same order of magnitude as the improvement in BAN. (FF 132-134.) The alleged superiority of the deletion in BSG (63-fold) was no more than one of degree compared to the results of Suzuki (25-fold), not a difference "in kind." This, combined with Dr. Arnold's concession that Suzuki alone provided the impetus to make the 179-180 deletion in BGG, demonstrates that the results, even if reliable, were not truly unexpected and would not have been surprising to one of ordinary skill in the art in 1995; thus, the Borchert Declaration does not overcome the admitted *prima facie* obviousness of the '031 Patent in light of Suzuki and the Bisgard-Frantzen PCT.

54. Moreover, compared to the thermoinactivation assays of Suzuki, the Borchert Declaration experiments were performed at a lower temperature; at a substantially (100-fold) lower concentration of calcium, which destabilizes the proteins; and without pre-heating of the buffer. (FF 104-106.) Novozymes did not, as required by MPEP § 716.02(e), identify or explain these differences to the PTO Examiner during prosecution of the '031 Patent. (FF 101.) Novozymes'

litigation-induced attempt to explain the differences (the experiments were intended to replicate industrial conditions) is not persuasive because, even if true, Novozymes presented its experiment in direct response to Suzuki's work, which was not conducted under so-called industrial conditions. And, limited evidence presented on this issue (FF 175-177) contradicts Novozymes' claim regarding industrial conditions, at least as to pre-heating of the buffer. Novozymes thus has not met its burden to explain all differences from Suzuki.

55. In addition, there are significant deficiencies in the design and execution of the experiments reported in the Borchert Declaration. Specifically, the experiment was not designed to avoid the "ramp-up" effect which has a significant effect on the short half-life of BAN wild type. This deficiency lead to an overstatement of the BAN wild type half-life which, in turn, resulted in an overstatement in the difference in the increase in thermostability of making the deletion in BAN versus BSG. (FF 108-131.) Dr. Borchert also improperly extrapolated the half-life of the BSG del sample beyond the last time point taken and improperly omitted measured data points from the BSG del analysis. (FF 116-120.) In view of these deficiencies, the data obtained by Dr. Borchert are unreliable and, at best, an overstatement of the effects of the deletion, because the difference in improvement was less than a factor of 2. (FF 133.) Thus, the Borchert Declaration does not reliably show sufficiently appreciable improvements to rebut the *prima facie* case of obviousness based on Suzuki and the Bisgard-Frantzen PCT.

56. Suzuki and the Bisgard-Frantzen PCT, taken together, teach more than enough to suggest to one of ordinary skill in protein engineering to make the 178/180 deletion in BSG, as Novozymes' own expert has admitted (and Novozymes has never denied). There are no meaningful differences between what Suzuki and the Bisgard-Frantzen PCT teach and the alleged invention of the '031 Patent, implicit in Novozymes' expert's admission that Suzuki renders obvious the '031 Patent. And, the sole evidence of non-obviousness offered by Novozymes in prosecution and at trial, the

Borchert Declaration and "experiment," is wholly unreliable. Therefore, the combination of Suzuki and the Bisgard-Frantzen PCT renders obvious the '031 Patent.

57. In view of Novozymes' admission that the claims are *prima facie* obvious in view of Suzuki and the Bisgard-Frantzen PCT and the failure of Novozymes to rebut this *prima facie* case, the Court finds that there is clear and convincing evidence that claims 1, 3, and 5 of the '031 Patent are invalid as obvious in view of Suzuki and the Bisgard-Frantzen PCT.

(c) *Machius '95 alone renders obvious the asserted claims*

58. Under 35 U.S.C. § 119, the claims of a United States patent are entitled to the benefit of the filing date of a foreign priority application only if that foreign application supports the claims in a manner required by 35 U.S.C. § 112, ¶ 1. *See In re Gosteli*, 872 F.2d 1008, 1010 (Fed. Cir. 1989).

59. Since the earliest-filed Novozymes' application describing use of the GAP (GCG) program, which Novozymes contends is necessary for construction of the term "% homology," is the PCT application No. PCT/DK96/00056, filed on February 5, 1996 (TE 101 at 2-3, A-7042–7043), the earliest possible effective date for claims 1, 3, and 5 is February 5, 1996. In addition, the earliest priority application to which the '031 Patent claims benefit and which discloses *Bacillus stearothermophilus* alpha-amylase and the amino acid sequence of SEQ ID NO:3 is the application filed on March 29, 1995. (FF 20-22.) Thus, regardless of the claim construction adopted by the Court, the earliest possible effective date for claims 1, 3, and 5 is March 29, 1995.

60. Because the Machius '95 paper was made publicly available at least as early as March 13, 1995 and the earliest possible priority date to which claims 1, 3, and 5 are entitled is March 29, 1995, the Machius '95 paper is prior art to the '031 Patent under 35 U.S.C. § 103(a). (FF 22.)

61. Machius '95 was not cited to the Examiner during the prosecution of the '031 Patent and, thus, Genencor's burden of proving obviousness is more easily carried. *See SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1355-56 (Fed. Cir. 2000).

62. In addition to summarizing and incorporating the teachings of Suzuki, which Novozymes' expert has conceded provided impetus to make the claimed 179/180 deletion in BSG, Machius '95 provides additional structural information increasing the motivation of the ordinarily skilled artisan to make the 179/180 deletion in BSG. (FF 68-74.) In particular, Machius '95 expressly teaches important structural information not found in Suzuki: (i) that the three-dimensional structures of BAA and BSG can be expected to be very similar to that of BLA; (ii) that Region I in BLA is in a loop on the surface of domain B; and (iii) that the loop is enlarged in BAA by two extra residues, which could cause increased mobility of this region and a decreased thermostability of the whole protein. (FF 68-74.)

63. One of ordinary skill in the art would not have needed the atomic coordinates to understand the teaching of Machius '95 that Region I is in a surface loop. (FF 80-82.) Thus, the fact that the atomic coordinates were not available from a public database as of the '031 Patent critical date does not detract from its teachings. Further, Novozymes' other attacks on the reliability of Machius '95 (on which paper Novozymes relied, when it suited its purposes) are rejected for the reasons set forth above.

64. The Machius '95 paper would have made it obvious to one of ordinary skill in the art in 1995 to make the deletion of amino acids 179 and 180 in BSG. By teaching that Suzuki Region I is in a surface loop, Machius '95 would have increased the motivation for the ordinarily skilled artisan to the make the deletion beyond what was provided by Suzuki. (FF 84.) The additional teachings of Machius '95 would have increased the expectation of the ordinarily skilled artisan that making the deletion in BSG would have increased the thermostability of BSG. (FF 85.)

65. The alleged unexpected results provided in the Borchert Declaration would not have been sufficient to rebut the even stronger case of obviousness presented by the Machius '95 paper, because the alleged results suffered from numerous deficiencies, including the failure to account for the ramp-up issue with BAN WT, improper extrapolation of half-lives, and omission of data. (FF 107-131.)

66. Novozymes' alleged unexpected results are also insufficient to rebut the finding of obviousness because Novozymes did not make any comparison to Machius '95, the closest prior art, which Novozymes failed to disclose to the PTO. *See In re Baxter*, 952 F.2d at 392; *In re Mayne*, 104 F.3d at 1341-1342; MPEP §§ 716.02(b), (c). Novozymes plainly did not meet its burden to explain and justify differences between its alleged unexpected results and Machius '95, because it never attempted to do so.

67. As explained above, the invention of the '031 Patent is obvious if, considering the scope and content of the prior art, the level of ordinary skill in the art, the differences between the alleged invention of the '031 Patent and the prior art, and any objective indicia of nonobviousness, a protein engineer of ordinary skill in the art would have been motivated to make the 179/180 deletion in BSG and would have had a reasonable expectation of success that in so doing the thermostability of BSG would be improved. *See In re Kahn*, 441 F. 3d at 987; *Graham*, 383 U.S. at 17-18; *In re O'Farrell*, 853 F.2d at 903-904. Taking all those factors together, the '031 Patent is demonstrably obvious in view of Machius '95. (There is no need to address the "motivation to combine" element of the *Graham* test with respect to Machius '95 alone.)

68. The problem confronted by a protein engineer and allegedly solved by the invention of the '031 Patent is increasing thermostability of the alpha-amylase of BSG. The '031 Patent solves that problem by essentially making a deletion of the RG amino acids at positions 179-180 of BSG, using SEQ ID NO:3 for numbering (differences between the asserted claims related to determination of

infringement, but the claims are consistent in the approach to the problem of thermostability, the 179-180 deletion).

69. Machius '95 addresses the same problem as the '031 Patent (*see, e.g.*, TE 173 at 551-553). As Novozymes has admitted, Machius '95 summarizes the teachings of Suzuki, which Novozymes has also admitted renders obvious the invention of the '031 Patent. Suzuki examined the effect on thermostability in BAN (comparing it to BLA) of a deletion corresponding to the 179-180 deletion in BSG of the '031 Patent. However, Machius '95 goes beyond Suzuki by teaching, as Novozymes also admits, that positions 179-180 are in an exposed surface loop and that shortening that loop would be likely to increase thermostability; while the structure studied in Machius '95 was that of BLA, Machius '95 expressly teaches that the three dimensional structures of BLA and BSG (which Machius '95 refers to as BStA) would be expected to be similar. (*See* generally FF 68-74, above).

70. Novozymes has already admitted that a protein engineer of ordinary skill in 1995 would be motivated to make the 179-180 deletion in BSG based on the teachings of Suzuki; indeed, Novozymes expert argues as much in attempting to diminish the important of Machius '95. As Dr. Machius testified, without any rebuttal from Novozymes, upon reading the teachings of Machius '95, an ordinarily skilled protein engineer would have had increased motivation to make the 179-180 deletion in BSG, and would also have had increased expectation of success (more than a "reasonably expectation," in fact – a "no-brainer," as Dr. Machius testified without rebuttal). (*See* FF 85, above.) This is because the teachings of Machius '95 address the concerns regarding areas of interaction in the structure of the enzyme that the protein engineer might have on reading Suzuki, but not after reading Machius '95. (*See id.*) Thus, Machius '95 alone renders obvious the invention of the '031 Patent.

71. Novozymes' only attacks on the teachings of Machius '95 (such as the availability of atomic coordinates and the teachings of Machius '98) are without merit, as explained in detail above (FF 77-82). The only remaining issue is whether any alleged secondary considerations of

nonobviousness rebut the finding of obviousness based on Machius '95. The only such secondary considerations offered by Novozymes are the alleged "unexpected results" set forth in the Borchert Declaration. As explained in detail above (FF 100-101), the Borchert Declaration fails to provide evidence of unexpected results sufficient to rebut the finding of obviousness of the '031 Patent, whether compared to Suzuki and the Bisgard-Frantzen PCT or the stronger, closer prior art of Machius '95. Thus, there is no evidence to rebut the finding of obviousness of the '031 Patent based on Machius '95 alone.

72. Based on the foregoing, there is clear and convincing evidence that based on either the combination of Suzuki and Bisgard-Frantzen or Machius '95 alone, it would have been obvious to an ordinarily skilled protein engineer in 1995 to make the alleged invention of the '031 Patent. Therefore, the '031 Patent is obvious. *See* 35 U.S.C. § 103(a); *In re Kahn*, 441 F.3d at 987; *Graham*, 383 U.S. at 13-14. Judgment is to be entered for Genencor.

(2) Asserted Claims 1 and 3 of the '031 Patent Are Invalid Because They Are Not Enabled

(a) *Legal standard*

73. 35 U.S.C. § 112 requires that a patent contain a written description of the invention that enables one skilled in the art to make and use the claimed invention. *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1212 (Fed. Cir. 1991) (citing *Atlas Powder Co. v. E.I. duPont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984)). Enablement of a claimed invention is a question of law. *See Amgen*, 927 F.2d at 1212 (citing *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1268 (Fed. Cir. 1986), *cert. denied*, 479 U.S. 1030 (1987)).

74. The enablement requirement demands that the scope of the claims bear a reasonable relationship to the scope of enablement provided by the specification. *See In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970). This requires that the "disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed

genus possess the disclosed utility." *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991). If the scope of a claim is greater than the disclosed support, the claim is invalid. *See* 35 U.S.C. § 112, ¶ 1. For DNA sequences, a sufficient disclosure must disclose how to make and use enough sequences to justify the grant of the claims sought. *See Amgen*, 927 F.2d at 1213.

75. In *Amgen, Inc. v. Chugai Pharm. Co.*, Amgen had claims that encompassed every possible analog of a gene containing about 4,000 nucleotides, with a disclosure only of how to make erythropoietin (EPO) and a few biologically active analogs from such genes. 927 F.2d at 1214. "The district court found that over 3,600 different EPO analogs can be made by substituting at only a single amino acid position, and over a million different analogs can be made by substituting three amino acids." *Id.* at 1213. The court succinctly summarized the facts and its conclusion:

> Considering the structural complexity of the EPO gene, the manifold possibilities for change in its structure, with attendant uncertainty as to what utility will be possessed by these analogs, we consider that more is needed concerning identifying the various analogs that are within the scope of the claim, methods for making them, and structural requirements for producing compounds with EPO-like activity. It is not sufficient, having made the gene and a handful of analogs whose activity has not been clearly ascertained, to claim all possible genetic sequences that have EPO-like activity.

Id. at 1214.

(b) *Claims 1 and 3 are not enabled*

76. There are approximately 10^{70} possible variants that are 95% homologous to SEQ ID NO:3 and contain the required double deletion of amino acid residues 179 and 180 that may or may not have alpha-amylase activity. (FF 231.) Of the 10^{70} possible variants, there are only a maximum of 1 in 10,000 amino acid sequences that are 95% homologous to SEQ ID NO:3 and contain the deletion of amino acid residues 179 and 180 of SEQ ID NO:3 that would have alpha-amylase activity. (FF 233-235.) Thus, one of skill in the art would need to select from an astronomically large number of possible variants to arrive at the small fraction of variants with alpha-amylase activity and, therefore, within claims 1 or 3.

77. The specification of the '031 Patent provides no general guidance as to which mutations in SEQ ID NO:3, other than a handful of mutations, will lead to proteins that are 95% homologous to SEQ ID NO:3, contain the required double deletion, and have alpha-amylase activity. (FF 236.) As Dr. Arnold stated at trial, "[p]roteins are both complex and finely tuned by evolution and they are quite complex machines such that changing even a single amino acid can often have a deleterious effect." (FF 233; Arnold, Tr. at 136:3-7, A-5137.) Thus, considering the complexity of proteins and the astronomically large number of possible variants that may or may not possess alpha-amylase activity, the Court finds that the specification of the '031 Patent does not provide sufficient disclosure to enable one of skill in the art to make the variants claimed in claims 1 and 3 without undue experimentation. The specification of the '031 Patent does not enable one of skill in the art to make and use the variants claimed in claims 1 and 3, without undue experimentation.

78. Accordingly, there is clear and convincing evidence claims 1 and 3 of the '031 Patent are not enabled and are invalid under 35 U.S.C. § 112, ¶ 1; judgment is to be entered for Genencor.

C. **The '031 Patent is Unenforceable**

(1) Novozymes Was Guilty of Inequitable Conduct in Prosecution of the '031 Patent

(a) *Legal standard for inequitable conduct*

79. Patent applicants have a duty to prosecute applications in the PTO with candor, good faith, and honesty. *See Precision Instrument Mfg. Co. v. Automotive Maint. Mach. Co.*, 324 U.S. 806, 818 (1945); *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1178 (Fed. Cir. 1995); *eSpeed, Inc. v. Brokertec USA, L.L.C.*, No. Civ.A. 03-612-KAJ, 2006 WL 416860, at *7 (D. Del. Feb. 22, 2006). This requirement is embodied in 37 C.F.R. § 1.56, which states that "[e]ach individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section." This duty extends to both patent applicants and

their attorneys. *See eSpeed*, 2006 WL 416860, at *7 (citing *FMC Corp. v. Manitowoc Co.*, 835 F.2d 1411, 1415 n.8 (Fed. Cir. 1987) ("'Applicant' as used here includes the patentee and the attorney who prosecute the application that resulted in the patent-in-suit, because the knowledge and actions of applicant's attorney are chargeable to applicant.")). Even if there is no evidence that the prosecuting attorney was aware of the falsity of a submission to the PTO, deceptive intent can be found on the sole basis of the inventor's conduct. *See Frazier v. Roessel Cine Photo Tech, Inc.*, 417 F.3d 1230, 1235-36 (Fed. Cir. 2005).

80. "Inequitable conduct includes affirmative misrepresentation of a material fact, failure to disclose material information, or submission of false material information, coupled with an intent to deceive." *See eSpeed*, 2006 WL 416860, at *7 (quoting *Molins PLC*, 48 F.3d at 1178).

81. A party alleging inequitable conduct must prove it by clear and convincing evidence. *Molins PLC*, 48 F.3d at 1178.

82. To prove inequitable conduct from a failure to disclose material prior art, a party "must offer clear and convincing proof of: (1) prior art or information that is material; (2) knowledge chargeable to applicant of that prior art or information and of its materiality; and (3) failure of the applicant to disclose the art or information resulting from an intent to mislead the PTO." *FMC Corp.*, 835 F.2d at 1415.

83. A party alleging inequitable conduct must show that "[t]he withholding of information [meets the] thresholds of both materiality and intent." *Molins PLC*, 48 F.3d at 1178. "[M]ateriality does not presume intent, which is a separate and essential component of inequitable conduct." *Allen Organ Co. v. Kimball Int'l, Inc.*, 839 F.2d 1556, 1567 (Fed. Cir. 1988). Once threshold levels of materiality and intent have been shown, a court must engage in "a careful balancing: when the misrepresentation or withheld information is highly material, a lesser quantum of proof is needed to establish the requisite intent. … In contrast, the less material the information, the greater the proof

must be." *Purdue Pharma L.P. v. Endo Pharm., Inc.*, 438 F.3d 1123, 1128-29 (Fed. Cir. 2006) (internal citations omitted).

84. PTO regulations help define what information is material to patentability. *See* 37 C.F.R. § 1.56; *Purdue Pharma L.P.*, 438 F.3d at 1128-29. The post-1992 regulations state that "information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and (1) [i]t establishes, by itself or in combination with other information, a *prima facie* case of unpatentability of a claim; or (2) [i]t refutes, or is inconsistent with, a position the applicant takes in: (i) [o]pposing an argument of unpatentability relied on by the Office, or (ii) [a]sserting an argument of patentability." 37 C.F.R. § 1.56(b). Additionally, withheld prior art may be material if a reasonable Examiner would have considered the prior art important in deciding whether to grant an application. *See Digital Control Inc. v. Charles Machine Works*, 437 F.3d 1309, 1318-19 (Fed. Cir. 2006). The MPEP expressly instructs prosecuting attorneys that, "[w]hen in doubt," it is the appropriate course to submit information to the PTO to avoid questions concerning the disclosure of material information. MPEP §§ 2004, 2001.04, 2001.05.

85. "Intent need not be proven by direct evidence; it is most often proven by a showing of acts, the natural consequences of which are presumably intended by the actor." *Molins PLC*, 48 F.3d at 1180. An intent to deceive can be found from submission of an affidavit containing material misstatements directed at the very "heart" of patentability and withholding of a contradictory article. *Pharmacia Corp. v. Par Pharmaceutical Inc.*, 417 F.3d 1369, 1371 (Fed. Cir. 2005).

86. While "materiality does not presume intent, which is a separate and essential component of inequitable conduct," *Allen Eng'g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1352 (Fed. Cir. 2002) (internal quotation marks and citation omitted), the materiality of a reference may lead to an inference of intent. *See Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs., Ltd.*, 394 F.3d 1348, 1354 (Fed. Cir. 2005) ("in the absence of a credible explanation, intent to deceive is generally

inferred from the facts and circumstances surrounding a knowing failure to disclose material information"). "Intent to deceive, however, cannot be 'inferred solely from the fact that information was not disclosed; there must be a factual basis for a finding of deceptive intent.'" *Purdue Pharma L.P.*, 438 F.3d at 1134 (quoting *Hebert v. Lisle Corp.*, 99 F.3d 1109, 1116 (Fed. Cir. 1996)). However, "a patentee facing a high level of materiality and clear proof that it knew or should have known of that materiality, can expect to find it difficult to establish 'subjective good faith' sufficient to present the drawing of an inference of intent to mislead." *Ferring B.V. v. Barr Labs., Inc.*, 437 F.3d 1181, 1191 (Fed. Cir. 2006) (quoting *Critikon, Inc. v. Becton Dickinson Vascular Access, Inc.*, 120 F.3d 1253, 1257 (Fed. Cir. 1997)). A persistent pattern of material misrepresentations on the part of the patentee can be tantamount to clear and convincing evidence of deceptive intent. *See PerSeptive Biosystems, Inc. v. Pharmacia Biotech, Inc.*, 225 F.3d 1315, 1320 (Fed. Cir. 2000). To defeat an inference of intent to deceive from withholding a reference, the reasons given must be "plausible." *Ferring B.V.*, 437 F.3d at 1191 n.11 (and citations).

87. Further, intent may be inferred "from the materiality of the affidavits, … the affirmative acts of submitting them, their misleading character, and the inability of the examiner to investigate the facts." *Paragon Podiatry Lab., Inc. v. KLM Labs., Inc.*, 984 F.2d 1182, 1190 (Fed. Cir. 1993). Affirmative misrepresentations are typically accorded a relatively high degree of materiality, from which intent may be inferred. *See Purdue Pharma L.P.*, 438 F.3d at 1133 (stating that the information therein "was material, but not as material as an affirmative misrepresentation would have been"); *Rohm & Haas Co. v. Crystal Chem. Co.*, 722 F.2d 1556, 1571 (Fed. Cir. 1983) ("In contrast to cases where allegations of fraud are based on the withholding of prior art, there is no room to argue that submission of false affidavits is not material."). An inference of intent may be deflected if the patentee presents to the Examiner previously withheld data. *See Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 972 (Fed. Cir. 2006).

(b) *Borchert and Garbell had a duty of candor in prosecuting the '031 Patent*

88. Dr. Borchert is an inventor of the '031 Patent, was present at the interview with the Examiner and was involved in developing the prosecution strategy of the '031 Patent. Mr. Garbell was the attorney who prosecuted the '031 Patent. (FF 30.) Thus, both Dr. Borchert and Mr. Garbell were involved with the prosecution of the '031 Patent and owed a duty of candor on its prosecution.

(c) *Inequitable conduct based on non-disclosure of Machius '95*

89. Machius '95 was not cited to the PTO during the prosecution of the '031 Patent and was not mentioned by either Dr. Borchert or Mr. Garbell during the interview with Examiner Prouty. (FF 47.)

90. At a minimum, Machius '95 provides highly material information not found in Suzuki and provides more motivation for the ordinary skilled artisan to make the deletion of 179 and 180 in BSG than the motivation provided by Suzuki. (FF 84-85.) Dr. Borchert himself admits that there was information provided by Machius '95 that was not found in Suzuki. (FF 75-76.) Additionally, Machius '95, alone, renders obvious the asserted claims of the '031 Patent. (FF 84-85.) And, critically, Mr. Garbell admitted that the '031 Patent might not have issued had Machius '95 been presented to the Examiner. (FF 98.) Thus, Machius '95 was not cumulative to Suzuki and was highly material to prosecution of the '031 Patent.

91. Dr. Borchert and Mr. Garbell were both very aware of the Machius '95 reference during prosecution of the '031 Patent. Dr. Borchert admits that he had read the Machius '95 paper closely after it was published, he invited Dr. Machius to give a seminar at Novozymes, incorporated a discussion of the reference into seminars he gave and papers he authored, and discussed Machius '95 extensively in a declaration submitted to the PTO and deposition given in connection with an interference pending at the very same time as the September 2004 interview with the Examiner and submission of the September 2004 amendment and Borchert Declaration. (FF 86-93.) Given Dr.

Borchert's extensive familiarity with and multiple citations to the Machius '95 reference, he knew or must have known of its materiality to the '031 Patent application.

92. Mr. Garbell testified that he discussed the Machius '95 reference extensively with Dr. Borchert during the prosecution of the '031 Patent. (FF 91-93.) In fact, Mr. Garbell linked in his own mind the disclosure in Machius '95 of Suzuki and the '031 Patent application. (FF 93.) Thus, Mr. Garbell was aware that the Machius '95 reference was relevant to the claims of the '031 Patent and material to its prosecution. Yet, even though Mr. Garbell was not a person of skill in the art (FF 96), and even though he was aware of the "when in doubt" rule requiring disclosure to the PTO in close cases, he never disclosed Machius '95 to the PTO.

93. With respect to Machius '95, Mr. Garbell now claims that he did not make any affirmative decision about citing or not citing Machius '95 (Garbell, Tr. at 442:5-21, A-5673), despite having extensively discussed the reference with inventors of the '031 Patent contemporaneously with the submission of the Amendment that led to the issuance of the '031 Patent, and despite having admitted that he recognized that Machius '95 at least summarized the teachings of Suzuki. (FF 91-93.) Notwithstanding his extensive discussions with Mr. Garbell about Machius '95 (FF 92), and even though Mr. Garbell reminded him that Machius '95 at least summarized Suzuki (FF 93), Dr. Borchert argues that Machius '95 is immaterial to the claims of the '031 Patent.

94. As described in detail above (*see*, *e.g.*, FF 41-44), Novozymes (including inventor Borchert and attorney Garbell), had substantial, contemporaneous commercial motivation, caused by the success of SPEZYME® Ethyl, to manipulate the patent process to obtain expedited issuance of the '031 Patent. Mr. Garbell's and Dr. Borchert's protestations of innocence, or at least of no affirmative intent to mislead, are not credible. Everything about Novozymes' prosecution of the '031 Patent, especially after the introduction of SPEZYME® Ethyl, demonstrates that Novozymes acted

intentionally in withholding Machius '95 (choosing instead to attack Suzuki, the weaker prior art and no longer the basis of any rejection).

95. After payment of the issue fee in the application that issued as the '031 Patent, the Examiner cited Machius '95 in the parent application. Even then, Novozymes did not withdraw the '031 Patent from issue in order to cite the Machius '95 reference in the '031 application. (FF 99.)

(d) *Inequitable conduct based on the Borchert Declaration and underlying experiments*

96. The reliability of the Borchert Declaration and experiment were central to prosecution and issuance of the '031 Patent. The Examiner relied on the alleged "in kind" magnitude of the relative improvement in BSG versus BAN to permit Novozymes to "take back" the narrow, stalling claims and allow issuance of broader claims. In particular, in the Notice of Allowability, she stated that although Novozymes' claims are *prima facie* obvious over Suzuki and the Bisgard-Frantzen PCT, the Borchert Declaration "establishes that the claimed variants exhibit unexpectedly large increases in thermostability when compared to the increases in thermostability obtained for the corresponding mutations taught by Suzuki *et al*." (FF 48.)

97. Dr. Borchert was aware that claims directed to a BSG with a deletion in amino acids 179 and 180 had been rejected over Suzuki and the Bisgard-Frantzen PCT. (FF 30-31.)

98. Dr. Borchert was aware going into the interview with Examiner Prouty that claims were likely going to issue on the basis of the Declaration, and that such claims were going to be asserted against Genencor. (FF 33, 39-40.)

99. Dr. Borchert had studied Suzuki in great detail, and thus was aware of how the conditions under which the studies underlying his Declaration were performed differed from those of Suzuki, including not preheating the buffer and using a calcium concentration that is 100-fold less than that of Suzuki. Using preheated buffer in a thermal inactivation assay has universally been known for at least 30 years. (FF 105.) Dr. Borchert knew that the low calcium levels he employed influenced

alpha-amylase stability. (FF 106.) Dr. Borchert knew the temperature of his experiment was materially different from Suzuki's. (FF 104.) Dr. Borchert thus knew or must have known that the conditions employed in his experiments would have resulted in an unreliable half-life for BAN WT.

100. Dr. Borchert knew that the Declaration did not contain the data points measured for BSG del at 2881 minutes and at 2940 minutes, and chose not to inform the Examiner that these data points had been omitted from the Declaration. (FF 121-131.)

101. Dr. Borchert testified that one of ordinary skill in the art could not have a specific expectation of the increase in thermostability in BSG relative to the increase in thermostability of BAN upon introduction of that same deletion. (FF 132.) This testimony casts doubt on the truthfulness of Dr. Borchert's and Mr. Garbell's assertions to the PTO that the magnitude of the increase in stability of BSGdel over BSG relative to the increase in stability of BANdel over BAN was "very surprising" and "significantly" and "substantially" greater than what would have been expected based on the combined teachings of Suzuki and the Bisgard-Frantzen PCT, or that the difference was one of "kind" and not merely one of "degree." (FF 133-134.)

102. Dr. Borchert and Mr. Garbell knew that a showing of unexpected results was crucial to the issuance of the '031 Patent. (FF 30-36.) Based on their interview with Examiner Prouty, Dr. Borchert and Mr. Garbell knew or must have known that the scope of the claims that the Examiner would allow depended on the magnitude of Dr. Borchert's "unexpected" results. (FF 45-46.) Dr. Borchert and Mr. Garbell asserted to the PTO that the Borchert Declaration evidenced "very surprising" and "unexpected" results, despite Dr. Borchert's admission that he had no expectation about the magnitude of thermostabilization in BSG prior to performing his experiments. (FF 46.) Dr. Borchert knew or must have known that the conditions he selected for the experiments underlying his Declaration would distort the magnitude of the thermostabilization of BSG relative to BAN upon

introduction of the Suzuki deletion (FF 104-120), and intentionally chose to remove data points from the BSG del half-life calculations without informing the PTO. (FF 121-131.)

103. Critically, Novozymes' "showing" of "unexpected results" was misleading because it was not made in comparison to Machius '95, which, as described above (FF 60-74), was the closest prior art, closer even than Suzuki and the Bizgard-Frantzen PCT. This violated Novozymes', and especially Mr. Garbell's, duty under MPEP §§ 716.02(b), (c) (described above, FF 97-98), and further demonstrated the misleading and intentional nature of Novozymes' conduct.

104. Mr. Garbell failed to exercise his duty as prosecuting attorney and therefore failed to fulfill his duty of candor to the PTO. Specifically, Mr. Garbell helped plan the Borchert experiment, but made no effort to inquire about, test or verify the data and conclusions presented in the Borchert Declaration. He also never disclosed to the PTO the many differences between the Borchert "experiment" and Suzuki, because he never made the required inquiry. This conduct violated Mr. Garbell's duty, described in MPEP §§ 716.01, *et seq.*, to assure that Novozymes' arguments of non-obviousness were supported by objective, factual evidence, and that the alleged unexpected results were presented in comparison to the closest prior art.

105. Based on the omissions and affirmative misrepresentations by Novozymes, which were the grounds for the Examiner's issuance of the '031 Patent, and the knowledge by Novozymes of the Examiner's reliance on these misrepresentations, coupled with Novozymes' clear motivation for a speedy issuance of the '031 Patent claims, and the many other factors identified above, it is clear Novozymes acted with deceptive intent in its representations to the PTO in and regarding the Borchert Declaration.

(e) *Novozymes committed inequitable conduct, rendering the '031 Patent unenforceable.*

106. As described in detail above, Dr. Borchert and Mr. Garbell were very aware of the Machius '95 during prosecution of the '031 Patent. Machius '95 was highly material to the '031

prosecution, providing significant teachings beyond Suzuki. Machius '95 was never disclosed to the Examiner during the '031 prosecution, nor is there any evidence the Examiner was aware of Machius '95 before the '031 claims were allowed and the issue fee paid.

107. Similarly, Dr. Borchert and Mr. Garbell knew or must have known of the numerous deficiencies in the Borchert Declaration and experiment. They did not disclose those deficiencies to the PTO, even though (or more likely because), the plan to manipulate the '031 prosecution and target Genencor depended on the Examiner accepting the alleged unexpected results.

108. In view of: the contemporaneous commercial motivation; the "Option" plan to first present, then take back, narrow claims to "buy time"; the high materiality of Machius '95; Dr. Borchert and Mr. Garbell's extensive familiarity with the reference; Novozymes' strong incentive to intentionally withhold it from the PTO; and Mr. Garbell's concession that had Machius '95 been disclosed the '031 Patent may not have issued, Mr. Garbell and Dr. Borchert's arguments are not credible or plausible. Novozymes acted with deceptive intent during prosecution of the '031 Patent, failing to disclose Machius '95 and omitting to disclose, and/or misrepresenting, the deficiencies in the Borchert Declaration and experiment.

109. Novozymes had every opportunity to attempt to "cure" its non-disclosures and misrepresentations by making full disclosure to the PTO before issuance of the '031 Patent. Novozymes never did so, nor did it withdraw the '031 Patent from issuance to permit it to attempt such a "cure," evidencing its deceptive intent. *Cf. eSpeed*, 2006 WL 416860, at *7. This final omission was especially important, given Mr. Garbell's admission that had Novozymes disclosed Machius '95, the '031 Patent might not have issued.

110. It is instructive to compare this case to *Kao Corp. v. Unilever*. In that case, a patentee had withheld from the Patent Office data obtained from comparative testing results but later presented that data to the Examiner; the Federal Circuit noted that there was evidence from which the trial court

could have found an intent to deceive, but chose not to disturb the trial court's finding that the ultimate submission to the Examiner of the previously withheld data deflected a finding of deceptive intent. 441 F.3d at 972. In stark contrast, Novozymes failed to take any effort to "cure" its nondisclosures and misleading presentation to the Examiner, even though Novozymes' Mr. Garbell admitted that the '031 Patent might not have issued had Machius '95, at least, been disclosed to the Examiner. The conclusion is inescapable – Novozymes acted with deceptive intent.

111. There is clear and convincing evidence that Novozymes omitted to disclose material prior art and made material misrepresentations (including omissions) in prosecution of the '031 Patent, acting with deceptive intent. Therefore, the '031 Patent was procured by means of inequitable conduct and is unenforceable; judgment is to be entered for Genencor.

(2) The '031 Patent is Unenforceable Due to Prosecution Laches

112. Prosecution laches is an equitable doctrine that may be applied to bar enforcement of patent claims following an unreasonable and unexplained delay in prosecution, even if the applicant technically complied with all pertinent statutes and rules. *See Symbol Techs., Inc. v. Lemelson Med.*, 277 F.3d 1361, 1363-68 (Fed. Cir. 2002). More than mere delay, egregious conduct which delays prosecution to the detriment of the public gives rise to prosecution laches. *See Intuitive Surgical, Inc. v. Computer Motion, Inc.*, No. Civ.A. 01-203-SLR, 2002 WL 31833867, at *3 (D. Del. Dec. 10, 2002) (quoting *In re Bogese*, 303 F.3d 1362, 1367 (Fed. Cir. 2002)); *Stambler v. RSA Security, Inc.*, 243 F. Supp. 2d 74, 76 (D. Del. 2003). Among the circumstances which indicate that a delay is unreasonable are broadening of claims leading to prejudice, *see MOSAID Techs. Inc. v. Samsung Elec. Co.*, 362 F. Supp. 2d 526, 552-53 (D.N.J. 2005), and unusual steps taken by the patentee to delay prosecution, *see Reiffin v. Microsoft Corp.*, 281 F. Supp. 2d 1149, 1151-52 (N.D. Cal. 2003).

113. The asserted claims in this case issued approximately ten years after the effective filing date of the '031 Patent. Even more important than this decade of prosecution is the fact that, as

explained in detail above (FF 30-40), Novozymes intentionally delayed prosecution of the '031 Patent, using the "Option 1/Option 2" plan to buy time so that it could obtain broader claims specifically targeted to Genencor. Compelled by its inability to compete with SPEZYME® Ethyl's superior performance, Novozymes' purpose in delaying prosecution was to obtain a patent with which to sue Genencor. Novozymes' egregious conduct resulted in the broadening of claims that eventually issued in the '031 Patent, causing prejudice to Genencor, which was forced to bear the risk, burden, and expense of this case.

114. There is clear and convincing evidence that the '031 Patent was obtained after an unreasonable and unexplained delay in prosecution, and is therefore unenforceable due to prosecution laches. Judgment is to be entered for Genencor.

D. **Genencor is Entitled to an Award of Attorneys' Fees**

115. "The court in exceptional cases may award reasonable attorney fees to the prevailing party," 35 U.S.C. § 285, whether the "prevailing party" is the patentee or the accused infringer. *Interspiro USA, Inc. v. Figgie Int'l Inc.*, 18 F.3d 927, 933-34 (Fed. Cir. 1994).

116. As described above, the Court has found that Genencor did not infringe the '031 Patent and that the '031 Patent is invalid and unenforceable. Thus, Genencor is the prevailing party.

117. "The determination of whether a case is exceptional and, thus, eligible for an award of attorney fees under [§] 285 is a two-step process. First, the district court must determine whether the case is exceptional....After determining that a case is exceptional, the district court must determine whether attorney fees are appropriate... ." *Phonometrics, Inc. v. Westin Hotel Co.*, 350 F.3d 1242, 1245 (Fed. Cir. 2003). *See also eSpeed*, 2006 WL 416860, at *15-16.

118. "The prevailing party may prove the existence of an exceptional case by showing: inequitable conduct before the PTO; litigation misconduct; vexatious, unjustified, and otherwise bad faith litigation; a frivolous suit or willful infringement." *Phonometrics,* 350 F.3d at 1245 (quoting

Epcon Gas Sys., Inc. v. Bauer Compressors, Inc., 279 F.3d 1022, 1034 (Fed. Cir. 2002). "Exceptional cases are normally those involving bad faith litigation or those involving inequitable conduct by the patentee in procuring the patent." *Brasseler, U.S.A. I., L.L.P. v. Stryker Sales Corp.*, 267 F.3d 1370, 1380 (Fed. Cir. 2001).

119. Genencor has shown by clear and convincing evidence that Novozymes committed inequitable conduct in procuring the '031 Patent. Thus, this is an exceptional case and this Court has discretion to award attorneys' fees to Genencor, pursuant to 35 U.S.C. § 285. *See A.B. Chance Co. v. RTE Corp.*, 854 F.2d 1307, 1312 (Fed. Cir. 1988).

120. To determine whether attorneys' fees are warranted, the Court "weighs considerations such as the closeness of the case, the tactics of counsel, the conduct of the parties, and any other factors that may contribute to a fair allocation of the burdens of litigation as between winner and loser." *S.C. Johnson & Son, Inc. v. Carter-Wallace, Inc.*, 781 F.2d 198, 201 (Fed. Cir. 1986). *See also Superior Fireplace Co v. Majestic Prods. Co.*, 270 F.3d 1358, 1378 (Fed. Cir. 2001); *National Presto Indus., Inc. v. West Bend Co.*, 76 F.3d 1185, 1197 (Fed. Cir. 1996).

121. This was not a close case. Genencor made a particularly strong showing of Novozymes' inequitable conduct in prosecuting the '031 Patent. Additionally, the question of obviousness was not close; Machius '95 alone plainly renders the '031 Patent obvious, Novozymes does not deny that Suzuki and the Bisgard-Frantzen PCT render the '031 Patent obvious, and Novozymes' own expert admitted that the "teachings" of the '031 Patent are obvious.

122. For all of these reasons, Novozymes' claims against Genencor were sufficiently without merit such that it would be unjust for Genencor to bear the expense of this litigation. Thus, an award of attorneys' fees to Genencor is appropriate.

IV. CONCLUSION/ORDER

Based on the findings and conclusions set forth above, judgment is to be entered in favor of Genencor and EDC, as follows:

1. Claims 1, 3, and 5 of the '031 Patent are not infringed;

2. Claims 1, 3, and 5 of the '031 Patent are invalid under 35 U.S.C. § 103(a);

3. The '031 Patent is unenforceable by reason of inequitable conduct and prosecution laches;

4. Genencor and EDC are entitled to their attorneys' fees because this is an exceptional case; and

5. Genencor and EDC are entitled to costs, as the prevailing parties.

Genencor is ordered to meet and confer with Novozymes and submit an appropriate form of judgment within two weeks of the date of this Order. Genencor is further ordered to submit its claim for attorneys' fees, and appropriate proof, within two weeks of the date of this Order; documentation submitted in support of the claim for attorneys' fees may be submitted confidentially, for *in camera* review by the Court.

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CERTIFICATE OF SERVICE

I, Donald E. Reid, hereby certify that on the 21st day of April, 2006, Defendants' Proposed Findings Of Fact And Conclusions Of Law was served by electronic filing upon counsel of record:

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